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(54) Title: PROCESS FOR PREPARATION OF PAROXETINE MALEATE

(57) Abstract

Paroxetine maleate is prepared substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl) piperidin-1-yl]butan-1,4-dioic acid by reaction of paroxetine free base with maleic acid at a temperature range below 40 °C, or using an alkanol, or ketone as solvent for the reaction, or an alkanol, hydrocarbon, ketone or ester solvent for recrystallization, or by a combination of suitable temperatures and solvents.

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PROCESS FOR PREPARATION OF PAROXETINE MALEATE

This invention relates to a novel process for preparing a pharmaceutically active compound. More specifically, the invention provides processes for preparing maleate salts of paroxetine free from a structurally similar impurity.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-) *trans* isomer of 4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxymethyl)piperidine. This compound is approved for use in therapy as the hydrochloride salt to treat *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

A particularly useful salt of paroxetine is the maleate. Example 2 of US 4,007,196 discloses the preparation of paroxetine maleate by crystallisation from ethanol/diethyl ether. Paroxetine maleate is now known to be obtainable both as a salt in which the ratio of paroxetine to maleic acid (by mole) is 1:1 and as a salt in which the ratio of paroxetine to maleic acid (by mole) is 2:1. Also the 1:1 salt has been found to exist in two polymorphic forms, referred to as Form A and Form B. The preparation of the 1:1 and 2:1 salts, and the polymorphs, is described in GB 9823856.1.

It has now been discovered that the known procedures for manufacturing paroxetine maleate give rise to substantial amounts (up to 30%) of an undesirable impurity, 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid, usually in the form of a salt, for example with paroxetine itself. The existence of this impurity is not easy to detect as a result of its chemical similarity to the desired paroxetine salt; it has not previously been mentioned in the literature, and no processes have been described for its prevention or removal.

This invention is based on the finding that paroxetine maleate may be prepared substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl) piperidin-1-yl]butan-1,4-dioic acid by reaction of paroxetine free base with maleic acid in a temperature range previously considered sub-optimal, or by the selection of suitable solvents for the reaction or recrystallization of the product, or by a combination of suitable temperatures and solvents.

Accordingly in one aspect the present invention provides a process for preparation of a paroxetine maleate salt substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-

methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid, which comprises reacting paroxetine free base with maleic acid in solution at a temperature below 40°C, and crystallising a maleate salt from the solution.

Hitherto a reaction temperature of above 70°C was thought to be advantageous. The disadvantages of crystallisation at low temperature are overcome by careful control of crystallisation conditions, including the addition of seeds of the desired salt or polymorph.

This procedure may be used to prepare the 2:1 salt and 1:1 salt by contacting appropriate stoichiometric amounts of the acid and paroxetine free base, and is preferably used with seeding for the preparation of Form B paroxetine 1:1 maleate.

In another aspect the present invention provides a process for preparation of a paroxetine maleate salt substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid, which comprises reacting paroxetine free base with maleic acid in solution in an alkanol or ketone solvent and crystallising a maleate salt from the solution.

Preferred solvents for the preparation of paroxetine maleate substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid are alcohols such as propan-2-ol, or ketones such as methyl isobutylketone or acetone.

A particularly suitable solvent is propan-2-ol, especially for the preparation of paroxetine 1:1 maleate Form A. Reaction of paroxetine and maleic acid in propan-2-ol gives paroxetine maleate Form A even at elevated temperatures with little or no impurity formation.

In a further aspect of the invention, a paroxetine maleate salt containing 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid is purified by crystallisation from an alkanol, or ketone solvent to give a paroxetine maleate containing low levels of impurity.

Solvents which can be used for the preparation of substantially pure paroxetine maleate may also be used for the purification of the impure salt by crystallisation. Surprisingly, some solvents which are not preferred for the preparation of pure paroxetine maleate, for example ethyl acetate, may be used successfully for purification. The required polymorphic form of paroxetine 1:1 maleate may be prepared by seeding with the

appropriate seed crystals prior to crystallisation, optionally by recrystallization from a different solvent after purification.

Product that is "substantially free" of the 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid impurity typically contains less than 5% of the impurity. Suitably low levels of the impurity are less than 2%, more preferably less than 1% and optimally less than 0.2%.

The paroxetine maleate may obtained as a solvate, when during isolation from solution it becomes associated with the solvent in which it is dissolved. Any such solvate forms a further aspect of this invention. Solvates may be returned to the unsolvated salt by heating, for example by oven-drying, or by treatment with a displacement solvent which does not form a solvate.

Paroxetine free base may be prepared according to the procedures generally outlined in US Patent No 4,007,196 and EP-B-0 223403. Maleic acid is commercially available.

A paroxetine maleate substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid obtainable by the processes of this invention forms another aspect of this invention, and may be used in therapy as a pharmaceutically acceptable salt of paroxetine.

The paroxetine maleate salt substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid of this invention, (hereinafter the "compound of the invention") may be used to treat and prevent the following disorders:

Alcoholism
Depression
Panic Disorder
Obesity
Migraine
Anorexia
Pre-Menstrual Syndrome (PMS)
Trichotillomania
Substance Abuse
Anxiety
Obsessive Compulsive Disorder
Chronic Pain
Senile Dementia
Bulimia
Social Phobia
Adolescent Depression
Dysthymia

These disorders are hereinafter referred to as "the Disorders".

The present invention further provides a method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a compound of the invention to a sufferer in need thereof.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of any one or more of the Disorders which comprises an admixture of a compound of the invention with a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of the invention for treating and/or preventing any one or more of the Disorders.

The present invention also provides the use of a compound of the invention in the manufacture of a medicament for treating and/or preventing any one or more of the Disorders.

Most suitably the present invention is applied to the treatment of depression, OCD and panic.

Compositions containing a compound of this invention may be formulated for administration by any route, and examples are oral, sub-lingual, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may, if desired, be designed to give slow release of the paroxetine salt.

The medicaments may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The composition is usually presented as a unit dose composition containing from 1 to 200mg of active ingredient calculated on a free base basis, more usually from 5 to 100mg, for example 10 to 50mg such as 10, 12.5, 15, 20, 25, 30 or 40mg by a human patient. Most preferably unit doses contain 20mg of active ingredient calculated on a free base basis. Such a composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400mg of active ingredient calculated on a free base basis. Most preferably the unit dose is taken once a day.

Preferred unit dosage forms include tablets or capsules.

The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing.

Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or preservative. These agents may be utilised in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.

Specific examples of pharmaceutical compositions include those described EP-B-0223403, and US 4,007,196 in which the products of the present invention may be used as the active ingredients.

The following Examples illustrate the present invention.

Example 1

Paroxetine maleate (140 g) containing approximately 30% 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid was suspended in ethyl acetate (800 ml) and heated at reflux for 30 minutes. The suspension was cooled to a few degrees below reflux temperature and filtered. The residual liquor was cooled slowly to ambient temperature and allowed to crystallise. Ultrasonication was used to increase the rate of crystallisation. The solid product was collected by filtration and dried under vacuum to give paroxetine maleate 1:1 Form B (52.55 g).

Example 2

Paroxetine base (0.72 g) in propan-2-ol was treated with maleic acid (0.17 g) at 40-50°C, and the mixture was stirred vigorously. A crystalline solid separated from the solution and was isolated by filtration to give paroxetine maleate 1:1 salt Form A free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid.

Example 3

Maleic acid (0.52 g) was added to a rapidly stirred solution of paroxetine in toluene (20 ml) at room temperature. Seed crystals of paroxetine maleate Form A were added and the

reaction mixture stirred vigorously. Paroxetine maleate free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid was isolated by filtration, washed with toluene and dried.

Example 4

A solution of paroxetine base in toluene (2.14 g in 30 ml) was added dropwise to a solution of maleic acid (0.8 g) in propan-2-ol over a 15 minute period. The reaction mixture was stirred vigorously whereupon crystallisation commenced, and the resulting suspension was stirred for 1 hour. The solid was collected by filtration washed with propan-2-ol (5 ml) and dried under vacuum to give paroxetine maleate (2.05 g) substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid.

CLAIMS

1. A process for preparation of a paroxetine maleate salt substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid, which comprises reacting paroxetine free base with maleic acid in solution at a temperature below 40°C, and crystallising a maleate salt from the solution.

2. A process according to claim 1, in which the reaction takes place in an alkanol, ester, hydrocarbon or ketone.

3. A process for preparation of a paroxetine maleate salt substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid, which comprises reacting paroxetine free base with maleic acid in solution in an alkanol, or ketone solvent, and crystallising a maleate salt from the solution.

4. A process according to claim 3, in which the reaction takes place at a temperature below 40°C.

5. A process according to any one of claims 1 to 4 in which the solvent is propan-2-ol, toluene, methyl isobutylketone or acetone.

6. A process for obtaining a paroxetine maleate salt substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid which comprises a) heating a paroxetine maleate salt containing 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid in a solvent, b) filtering the hot solution, and c) cooling the solution to induce crystallisation.

7. A process according to claim 6 wherein the solvent is a hydrocarbon, ketone, alkanol or ester solvent.

8. A process according to claim 7 in which the solvent is propan-2-ol, toluene, methyl isobutylketone, acetone or ethyl acetate.

9. A paroxetine maleate salt substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid.

10. A pharmaceutical composition for use in the treatment and/or prevention of any one or more of the Disorders which comprises a compound according to claim 9 or a product of the process of any one of claims 1 to 8, together with a pharmaceutically acceptable carrier.

11. A method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a compound according to claim 9 or a product of the process of any one of claims 1 to 8, to a sufferer in need thereof.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/22 C07D405/12 A61K31/445 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	WO 99 52901 A (SMITHKLINE BEECHAM PLC) 21 October 1999 (1999-10-21) cited in the application the whole document	1
A	EP 0 223 403 A (BEECHAM GROUP PLC) 27 May 1987 (1987-05-27) cited in the application the whole document	1
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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